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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/20/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/673,302	LAW ET AL.	
	Examiner	Art Unit	
	Thai-An N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-92* is/are rejected.

7)☒ Claim(s) *92* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' Amendment, filed 1/27/03, Paper No. 17, has been entered. Claims 1-68 have been cancelled. Claims 69-92 have been added.

The request filed on 1/27/03 for a Request for Continued Examination (RCE) under 37 CFR 1.114 is acceptable and a RCE has been established. An action on the RCE follows.

Claims 69-92 are pending and being examined on the merits.

Any rejection made of record in the prior Office action, mailed 7/29/02, Paper No. 13, and not made of record in the instant Office action, has been withdrawn in view of Applicants amendments to the claims.

Sequence Compliance

Applicants' submission of the Sequence Listing, Computer Readable Copy and/or Amendment, filed on 1/23/03, Paper No. 21, is proper and has been entered.

Specification

The objection to the specification under 35 U.S.C. 132, with regard to new matter, is *withdrawn* in view of Applicants' arguments and/or amendments.

Claim Objections

Claim 92 objected to because of the following informalities: The claim has been labeled "*h)*". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1-68, under 35 U.S.C. § 112, 1st ¶, with regard to new matter, is *withdrawn* in view of Applicants' arguments and/or amendments to the claims.

Claims 69-92 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record advanced on pages 6-8 of the prior Office action, mailed 7/29/02. This is a written description rejection.

Applicants argue that the claims as amended now meet the combination of limitations the Examiner has stated in the written description provision of 35 U.S.C. §112. Applicants argue that the present invention is directed to transgenic mice which have been engineered to express a GP IIIa protein which has one or more of its cytoplasmic domain tyrosine residues replaced with a residue that is non-phosphorylatable. To produce the transgenic mice of the invention, Applicants argue, it is only required that one of these tyrosine sites of phosphorylation be

replaced with a residue which is non-phosphorylatable. Applicants argue that those of skill in the art would readily be able to identify residues that are phosphorylatable and those which would not be. As such, Applicants argue that there is no requirement to list each of the non-phosphorylatable amino acids in the present application. See pp. 9-10, bridging ¶, of the Response.

Applicants' arguments have been considered, however they are not found to be persuasive. In particular, it is maintained that written description is provided for residues 747 and 759 of SEQ ID NO: 1; however, the prior written description rejection of the instant invention is directed to the fact that the only described mutant mouse GP IIIa gene, where the mutant gene encodes for a GP IIIa protein having a cytoplasmic domain tyrosine residue replaced with a non-phosphorylatable residue are residues 747 and 759 of SEQ ID NO: 1, which has been replaced with a phenylalanine residue, meet the written description provision of 35 U.S.C. § 112. The specification fails to provide adequate written description for the breadth of the claims. The specification fails to provide specific teachings or guidance to provide description for any other cytoplasmic domain tyrosine residues which have been replaced with a non-phosphorylatable residue, other than the described 747 and 759 residues of SEQ ID NO: 1. For example, it is well-known in the art that the tertiary structure of a protein is highly affected by its residues. The specification fails to provide teachings as to which tyrosine residues, other than the described 747 and 759 of SEQ ID NO: 1 would be considered cytoplasmic once the protein was folded. The specification does not teach or suggest the replacement of other tyrosine

residues [aside from 747 and 759] to produce a mutant GP IIIa gene. Specifically, the specification teaches that the phosphorylation of two tyrosine residues at positions 747 and 759 are important for normal integrin/cytoskeletal interactions [see pp. 4-5 of the specification]. The skilled artisan cannot envision all such mutant GP IIIa genes, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Claims 69-92 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record advanced on pages 8-12 of the prior Office action.

The specification teaches the production and use of a transgenic mammal in which the endogenous GP IIIa gene (also known as β3) has been replaced in whole or in part with a mutant GP IIIa gene, where one or both of the two phosphorylatable cytoplasmic tyrosine residues have been replaced with non-tyrosine residues (see p. 1, lines 11-17). The specification specifically teaches that the murine GP IIIa gene was isolated and the two tyrosine residues 747 and 759

were mutated to phenylalanine using standard site-directed mutagenesis (see examples 1-2). The specification teaches that the mutated GP IIIa DNA was then subcloned into a targeting vector containing a neomycin resistant cassette, and the neo^r DNA was flanked by FRT recognition sequences (see example 3). The targeting construct was then transfected into murine ES cells and positive clones were identified (see example 4). The ES cells that contained the mutant GP IIIa DNA were then injected into blastocysts and implanted into pseudo-pregnant foster mothers. The male chimeric mice were identified and mated with wild-type females. The heterozygote offspring were then further mated to produce homozygote animals. The specification teaches that the resulting mice are viable and express GP IIB-IIIa on their platelets at similar levels to that seen in normal animals expressing non-mutant GP IIIa (see p. 22, lines 8-12).

Applicants argue that, with regard to Exhibit A, the Examiner is confused, as the mice of Law *et al.* are the same mice as that of the present invention. As such, the Law Exhibit, which describes transgenic mice which contain an αIIbβ3 transgene and exhibit a phenotype of defective platelet aggregation and clot retraction responses *in vitro* and an *in vivo* bleeding defect, confirms the phenotype taught by Applicants in the instant application. See pp. 10-11 of the Response.

Applicants' arguments have been carefully considered, however, they are not found to be persuasive. Upon further review of the Law Exhibit, the Examiner agrees that the transgenic mice described in the exhibit are those of the instant invention. However, the exhibit teaches that platelets, which were isolated from

mice that were homozygous for the mutant β3 gene, failed to aggregate when stimulated with 0.05 units ml^{-1} of thrombin, and formed unstable aggregates when stimulated with 0.1 units ml^{-1} of thrombin. See p. 808-809, bridging ¶. As such, it would appear that the mice of the instant invention have decreased platelet aggregation. The specification teaches that mice of the instant invention, "will display non-normal platelet aggregation." See p. 18, line 18. However, the specification fails to provide specific support for a phenotype of decreased platelet aggregation, as the term "non-normal" as broadly recited in the specification encompasses, for example, hyper-aggregation as well as deficient aggregation. It is well-known in the art that mutations in a gene can cause both gain of function as well as loss of function. If Applicant feels that support for the phenotype of decreased platelet aggregation is to be found in the specification, Applicant is invited to point specifically in the specification, by page and line number, where such support may be found. As such, at the time of filing, the instant invention was not enabled because Applicants did not appreciate the instant invention, and do not teach how to use the claimed invention.

Furthermore, it is reiterated that the specification has not provided an enabling disclosure for the claimed transgenic mice. However, the specification *fails* to provide an enabling disclosure for the preparation of the claimed transgenic mice exhibiting an appropriate phenotype for reasons of record [see prior Office action, p. 10 and pp. 6-12 of the Office action mailed 8/2/01, Paper No. 5]. The state of the art of transgenesis is such that it would not that resulting phenotype of the transgenic

animal are directly dependent on the specific transgene construct. Because the specification discloses no phenotype for the transgenic mice, undue experimentation would have been required for one of skill in the art to make and/or use the claimed invention. To this end, the specification does not provide guidance for any particular phenotype for the claimed transgenic mice, other than the anticipated expression of the transgene. Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification fails to provide an enabled use for the claimed mice without a resulting phenotype. However, the specification fails to provide teachings or guidance such that those skilled in the art would know how to make and use the full scope of the claimed invention without undue experimentation.

Accordingly, in view of the quantity of experimentation necessary for the production and methods of use of the claimed transgenic mice and the unpredictable and undeveloped state of the transgenic, and particularly with respect to the unpredictable nature of the phenotypic effect, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 69-73, 77, 80, 83-86 and 89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 69, as written is vague and indefinite. Firstly, the claim recites that the transgenic mouse comprises a mutant GP IIIa gene. A transgenic mouse would require the transgene to be integrated into its genome. A mouse that comprises a mutant GP IIIa gene encompasses a chimeric mouse, or a xenograft mouse. As such, this claim language does not reflect the claimed invention. Furthermore, it is unclear if the the gene that has had a cytoplasmic domain tyrosine residue replaced is the mutant GP IIIa gene or the wild-type GP IIIa gene. Appropriate correction is required. Claims 70 and 71 depend from claim 69.

Claims 70, 73, 77, 80, 84, 89, as written, are vague and indefinite. The claims recites that the tyrosine residue is 747 or 759. This is unclear because the numbering of residues would depend upon which sequence (and whose sequence) the residue would be from. Furthermore, it is unclear if the residue that is replaced would be from the mutant or wild-type gene.

Claim 72, as written, is vague and indefinite. The claim recites that the transgenic mouse comprises a mutant GP IIIa gene. A transgenic mouse would require the transgene to be integrated into its genome. A mouse that comprises a mutant GP IIIa gene encompasses a chimeric mouse, or a xenograft mouse. As such, this claim language does not reflect the claimed invention. Claims 73 and 74 depend from claim 72.

Claim 83, as written, is incomplete. The claim recites that transfected embryonic stem cells would be used to generate a transgenic mouse. This claim is incomplete, as it would require more than ES cells to generate a mouse. For example, the cells would have to be introduced into a surrogate mother, developed and brought to term before a transgenic mouse would be generated. Appropriate correction is required. Claims 84-86 depend from claim 83.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 75 and 82 rejected under 35 U.S.C. 102(b) as being anticipated by Zhou *et al.* [Blood. 89:1551-1559, March 1, 1997].

The claims are directed to platelets isolated from the blood plasma of the transgenic mouse of claim 69 and claim 76, respectively.

Zhou teach that 700 to 900 μL of whole blood was collected from wild-type mice and platelets were isolated and counted. See p. 1552, 2nd column, *Mouse platelet aggregometry.*

Note that with regard to the claims, the mice from which the platelets are isolated from do not require a phenotype. Furthermore, neither mouse [of claim 69,

or claim 76] recites a phenotype, nor do the claims recite that the mice are homozygotes. For example, the mouse of claim 69 could be a chimeric or xenograft mouse, and the mouse of claim 76 could be a heterozygous mouse. Therefore, platelets isolated from such mice could be wild-type platelets.

As such, the platelets as taught by Zhou anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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